REMARKS

In its Decision on Appeal ("Decision") mailed August 20, 2003, the Board of Patent Appeals and Interferences ("Board") affirmed the Examiner's final rejection of claims 24 - 27 and 29 - 33[1] under 35 U.S.C. § 101, and derivatively under 35 U.S.C. § 112, first paragraph, for lack of utility, but on grounds different from those relied upon by the Examiner in the final rejection mailed December 5, 2000. Pursuant to 37 C.F.R. § 1.196(b)(1), Appellants file herewith a showing of facts, amendments to the claims, and remarks.[2]

Appellants' Showing of Facts Fully Satisfies the Board's Evidentiary Concern, Proving That Uses of Appellants' Claimed Polynucleotides And Microarray In Expression Profiling Analyses Were Well-Established Prior To Appellants' Filing Date

Acknowledging the unrebutted statements in Appellants' Brief ("Brief") that the "[u]se of human polynucleotides and their encoded polypeptides as tools for toxicology testing, drug discovery, and the diagnosis of disease is 'well-established,'" Brief at 7, the Board nonetheless raises the evidentiary concern that "the references that Appellants cite to show the 'well-established' nature of these utilities were all published after the filing date of the instant application," Decision at 17.

In response, Appellants file herewith four expert Declarations under 37 C.F.R. § 1.132, with respective attachments, and ten (10) scientific references that were published prior to the filing date of the instant application. This showing of facts fully satisfies the Board's evidentiary concerns, establishing that, prior to the filing date of the instant application, it was well-established in the art that:

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[1] Pursuant to a prior election of species, each claim has been examined solely with respect to the species of SEQ ID NO:25 (protein sequence) and SEQ ID NO:102 (nucleic acid sequence).

[2] As a preliminary remark, Appellants note with appreciation the Board's decision to designate the affirmance as a new ground of rejection, affording Appellants an opportunity to respond fully.

polynucleotides derived from nucleic acids expressed in one or more tissues and/or cell types can be used as hybridization probes -- that is, as tools -- to survey for and to measure the presence, the absence, and the amount of expression of their cognate gene;

with sufficient length, at sufficient hybridization stringency, and with sufficient wash stringency -- conditions that can be routinely established -- expressed polynucleotides, used as probes, generate a signal that is specific to the cognate gene, that is, produce a gene-specific expression signal;

expression analysis is useful, *inter alia*, in drug discovery and lead optimization efforts, in toxicology, particularly toxicology studies conducted early in drug development efforts, and in phenotypic characterization and categorization of cell types, including neoplastic cell types;

each additional gene-specific probe used as a tool in expression analysis provides an additional gene-specific signal that could not otherwise have been detected, giving a more comprehensive, robust, higher resolution, statistically more significant, and thus more useful expression pattern in such analyses than would otherwise have been possible;

biologists, such as toxicologists, recognize the increased utility of more comprehensive, robust, higher resolution, statistically more significant results, and thus want each newly identified expressed gene to be included in such an analysis;

nucleic acid microarrays increase the parallelism of expression measurements, providing expression data analogous to that provided by older, lower throughput techniques, but at substantially increased throughput;

accordingly, when expression profiling is performed using microarrays, each additional gene-specific probe that is included as a signaling component on this analytical device increases the detection range, and thus versatility, of this research tool;

biologists, such as toxicologists, recognize the increased utility of such improved tools, and thus want a gene-specific probe to each newly identified expressed gene to be included in such an analytical device;

the industrial suppliers of microarrays recognize the increased utility of such improved tools to their customers, and thus strive to improve salability of their microarrays by adding each newly identified expressed gene to the microarrays they sell;

> it is not necessary that the biological function of a gene be known for measurement of its expression to be useful in drug discovery and lead optimization analyses, toxicology, or molecular phenotyping experiments;
>
> failure of a probe to detect changes in expression of its cognate gene does not diminish the usefulness of the probe as a research tool; and
>
> failure of a probe completely to detect its cognate transcript in any single expression analysis experiment does not deprive the probe of usefulness to the community of users who would use it as a research tool.

The Declarations being sufficiently brief, Appellants commend them in their entireties to the Examiner's attention and devote further comment here to identifying for the Examiner's convenience certain representative passages of the references filed herewith:

WO 95/21944 ("Differentially expressed genes in healthy and diseased subjects"), published August 17, 1995, describes the use of microarrays in expression profiling analyses, emphasizing that *patterns* of expression can be used to distinguish healthy tissues from diseased tissues and that *patterns* of expression can additionally be used in drug development and toxicology studies, without knowledge of the biological function of the encoded gene product. In particular, and with emphasis added:

> The present invention involves . . . methods for diagnosing diseases . . . characterized by the presence of [differentially expressed] . . . genes, despite the absence of knowledge about the gene or its function. The methods involve the use of a composition suitable for use in hybridization which consists of a solid surface on which is immobilized at pre-defined regions thereon a plurality of defined oligonucleotide/ polynucleotide sequences for hybridization. Each sequence comprises a fragment of an EST. . . . Differences in hybridization patterns produced through use of this composition and the specified methods enable diagnosis of diseases based on differential expression of genes of unknown function . . . . [abstract]
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> The method [of the present invention] involves producing and comparing hybridization patterns formed between samples of expressed mRNA or cDNA polynucleotide sequences . . . and a defined set of oligonucleotide/polynucleotide[] . . . immobilized on a support. Those defined [immobilized] oligonucleotide/polynucleotide sequences are representative of the total expressed genetic component of the cells, tissues, organs or organism as defined by the collection of partial cDNA sequences (ESTs). [page 2]

The present invention meets the unfilled needs in the art by providing methods for the . . . use of gene fragments and genes, even those of unknown full length sequence and unknown function, which are differentially expressed in a healthy animal and in an animal having a specific disease or infection by use of ESTs derived from DNA libraries of healthy and/or diseased/infected animals. [page 4]

Yet another aspect of the invention is that it provides . . . a means for . . . monitoring the efficacy of disease treatment regimes including . . . toxicological effects thereof." [page 4]

It has been appreciated that one or more differentially identified EST or gene-specific oligonucleotide/polynucleotides define a pattern of differentially expressed genes diagnostic of a predisease, disease or infective state. A knowledge of the specific biological function of the EST is not required only that the EST[] identifies a gene or genes whose altered expression is associated reproducibly with the predisease, disease or infectious state. [page 4]

As used herein, the term 'disease' or 'disease state' refers to any condition which deviates from a normal or standardized healthy state in an organism of the same species in terms of differential expression of the organism's genes. . . [whether] of genetic or environmental origin, for example, an inherited disorder such as certain breast cancers. . . .[or] administration of a drug or exposure of the animal to another agent, e.g., nutrition, which affects gene expression. [page 5]

As used herein, the term 'solid support' refers to any known substrate which is useful for the immobilization of large numbers of oligonucleotide/polynucleotide sequences by any available method . . . [and includes, inter alia,] nitrocellulose, . . . glass, silica. . . . [page 6]

By 'EST' or 'Expressed Sequence Tag' is meant a partial DNA or cDNA sequence of about 150 to 500, more preferably about 300, sequential nucleotides. . . . [page 6]

One or more libraries made from a single tissue type typically provide at least about 3000 different (i.e., unique) ESTs and potentially the full complement of all possible ESTs representing all cDNAs e.g., 50,000 – 100,000 in an animal such as a human. [page 7]

The lengths of the defined oligonucleotide/ polynucleotides may be readily increased or decreased as desired or needed. . . . The length is generally guided by the principle that it should be of sufficient length to insure that it is on[] average only represented once in the population to be examined. [page 7]

Comparing the . . . hybridization patterns permits detection of those defined oligonucleotide/ polynucleotides which are differentially expressed between the

> healthy control and the disease sample by the presence of differences in the hybridization patterns at pre-defined regions [of the solid support]. [page 13]
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> It should be appreciated that one does not have to be restricted in using ESTs from a particular tissue from which probe RNA or cDNA is obtained[;] rather any or all ESTs (known or unknown) may be placed on the support. Hybridization will be used [to] form diagnostic patterns or to identify which particular EST is detected. For example, all known ESTs from an organism are used to produce a 'master' solid support to which control sample and disease samples are alternately hybridized. [page 14]
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> Diagnosis is accomplished by comparing the two hybridization patterns, wherein substantial differences between the first and second hybridization patterns indicate the presence of the selected disease or infection in the animal being tested. Substantially similar first and second hybridization patterns indicate the absence of disease or infection. This[,] like many of the foregoing embodiments[,] may use known or unknown ESTs derived from many libraries. [page 18]
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> Still another intriguing use of this method is in the area of monitoring the effects of drugs on gene expression, both in laboratories and during clinical trials with animal[s], especially humans. [page 18]

WO 95/20681 ("Comparative Gene Transcript Analysis"), filed in 1994 by Appellants' assignee and published August 3, 1995, has three issued U.S. counterparts: U.S. Pat. Nos. 5,840,484, issued November 24, 1998; 6,114,114, issued September 5, 2000; and 6,303,297, issued October 16, 2001.

The specification describes the use of transcript expression *patterns,* or "images", each comprising multiple pixels of gene-specific information, for diagnosis, for cellular phenotyping, and in toxicology and drug development efforts. The specification describes a plurality of methods for obtaining the requisite expression data -- one of which is microarray hybridization -- and equates the uses of the expression data from these disparate platforms. In particular, and with emphasis added:

> The invention provides a "method and system for quantifying the relative abundance of gene transcripts in a biological specimen. . . . [G]ene transcript imaging can be used to detect or diagnose a particular biological state, disease, or condition which is correlated to the relative abundance of gene transcripts in a given cell or population of cells. The invention provides a method for comparing the gene transcript image analysis from two or more different biological specimens

in order to distinguish between the two specimens and identify one or more genes which are differentially expressed between the two specimens." [abstract]

"[W]e see each individual gene product as a 'pixel' of information, which relates to the expression of that, and only that, gene. We teach herein [] methods whereby the individual 'pixels' of gene expression information can be combined into a single gene transcript 'image,' in which each of the individual genes can be visualized simultaneously and allowing relationships between the gene pixels to be easily visualized and understood." [page 2]

"The present invention avoids the drawbacks of the prior art by providing a method to quantify the relative abundance of multiple gene transcripts in a given biological specimen. . . . The method of the instant invention provides for detailed diagnostic comparisons of cell profiles revealing numerous changes in the expression of individual transcripts." [page 6]

"High resolution analysis of gene expression be used directly as a diagnostic profile. . . . " [page 7]

"The method is particularly powerful when more than 100 and preferably more than 1,000 gene transcripts are analyzed." [page 7]

"The invention . . . includes a method of comparing specimens containing gene transcripts." [page 7]

"The final data values from the first specimen and the further identified sequence values from the second specimen are processed to generate ratios of transcript sequences, which indicate the differences in the number of gene transcripts between the two specimens." [i.e., the results yield analogous data to microarrays] [page 8]

"Also disclosed is a method of producing a gene transcript image analysis by first obtaining a mixture of mRNA, from which cDNA copies are made." [page 8]

"In a further embodiment, the relative abundance o the gene transcripts in one cell type or tissue is compared with the relative abundance of gene transcript numbers in a second cell type or tissue in order to identify the differences and similarities." [page 9]

"In essence, the invention is a method and system for quantifying the relative abundance of gene transcripts in a biological specimen. The invention provides a method for comparing the gene transcript image from two or more different biological specimens in order to distinguish between the two specimens. . . . " [page 9]

"[T]wo or more gene transcript images can be compared and used to detect or diagnose a particular biological state, disease, or condition which is correlated to the relative abundance of gene transcripts in a given cell or population of cells." [pages 9 – 10]

"The present invention provides a method to compare the relative abundance of gene transcripts in different biological specimens. . . . This process is denoted herein as gene transcript imaging. The quantitative analysis of the relative abundance for a set of gene transcripts is denoted herein as 'gene transcript image analysis' or 'gene transcript frequency analysis'. The present invention allows one to obtain a profile for gene transcription in any given population of cells or tissue from any type of organism." [page 11]

"The invention has significant advantages in the fields of diagnostics, toxicology and pharmacology, to name a few." [page 12]

"[G]ene transcript sequence abundances are compared against reference database sequence abundances including normal data sets for diseased and healthy patients. The patent has the disease(s) with which the patient's data set most closely correlates." [page 12]

"For example, gene transcript frequency analysis can be used to different normal cells or tissues from diseased cells or tissues. . . ." [page 12]

"In toxicology, . . . [g]ene transcript imaging provides highly detailed information on the cell and tissue environment, some of which would not be obvious in conventional, less detailed screening methods. The gene transcript image is a more powerful method to predict drug toxicity and efficacy. Similar benefits accrue in the use of this tool in pharmacology. . . . " [page 12]

"In an alternative embodiment, comparative gene transcript frequency analysis is used to differentiate between cancer cells which respond to anti-cancer agents and those which do not respond." [page 12]

"In a further embodiment, comparative gene transcript frequency analysis is used . . . for the selection of better pharmacologic animal models." [page 14]

"In a further embodiment, comparative gene transcript frequency analysis is used in a clinical setting to give a highly detailed gene transcript profile of a diseased state or condition." [page 14]

"An alternate method of producing a gene transcript image includes the steps of obtaining a mixture of test mRNA and providing a representative array of unique probes whose sequences are complementary to at least some of the test mRNAs. Next, a fixed amount of the test mRNA is added to the arrayed probes. The test mRNA is incubated with the probes for a sufficient time to allow hybrids

of the test mRNA and probes to form. The mRNA-probe hybrids are detected and the quantity determined." [page 15]

"[T]his research tool provides a way to get new drugs to the public faster and more economically." [page 36]

"In this method, the particular physiologic function of the protein transcript need not be determined to qualify the gene transcript as a clinical marker." [page 38]

"[T]he gene transcript changes noted in the earlier rat toxicity study are carefully evaluated as clinical markers in the followed patients. Changes in the gene transcript image analyses are evaluated as indicators of toxicity by correlation with clinical signs and symptoms and other laboratory results. . . . The . . . analysis highlights any toxicological changes in the treated patients." [page 39]

U.S. Pat. No. 5,569,588 ("Methods for Drug Screening") ("the '588 patent"), issued October 29, 1996, with a priority date of August 1995, describes an expression profiling platform, the "genome reporter matrix", which is different from nucleic acid microarrays. Additionally describing use of nucleic acid microarrays, the patent makes clear that the utility of comparing multidimensional expression datasets is independent of the methods by which such profiles are obtained. The patent speaks clearly to the usefulness of such expression analyses in drug development and toxicology, particularly pointing out that a gene's failure to change in expression level is a useful result. Thus, with emphasis added,

The invention provides "[m]ethods and compositions for modeling the transcriptional responsiveness of an organism to a candidate drug. . . . [The final step of the method comprises] comparing reporter gene product signals for each cell before and after contacting the cell with the candidate drug to obtain a drug response profile which provides a model of the transcriptional responsiveness of said organism to the candidate drug." [abstract]

"The present invention exploits the recent advances in genome science to provide for the rapid screening of large numbers of compounds against a systemic target comprising substantially all targets in a pathway [or] organism." [col. 1]

"The ensemble of reporting cells comprises as comprehensive a collection of transcription regulatory genetic elements as is conveniently available for the targeted organism so as to most accurately model the systemic transcriptional response. Suitable ensembles generally comprise thousands of individually reporting elements; preferred ensembles are substantially comprehensive, i.e.

provide a transcriptional response diversity comparable to that of the target organism. Generally, a substantially comprehensive ensemble requires transcription regulatory genetic elements from at least a majority of the organism's genes, and preferably includes those of all or nearly all of the genes. We term such a substantially comprehensive ensemble a genome reporter matrix." [col. 2]

"Drugs often have side effects that are in part due to the lack of target specificity. . . . [A] genome reporter matrix reveals the spectrum of other genes in the genome also affected by the compound. In considering two different compounds both of which induce the ERG10 reporter, if one compound affects the expression of 5 other reporters and a second compound affects the expression of 50 other reports, the first compound is, a priori, more likely to have fewer side effects." [cols. 2 - 3]

"Furthermore, it is not necessary to know the identity of any of the responding genes." [col. 3]

"[A]ny new compound that induces the same response profile as [a] . . . dominant tubulin mutant would provide a candidate for a taxol-like pharmaceutical." [col. 4]

"The genome reporter matrix offers a simple solution to recognizing new specificities in combinatorial libraries. Specifically, pools of new compounds are tested as mixtures across the matrix. If the pool has any new activity not present in the original lead compound, new genes are affected among the reporters." [col. 4]

" A sufficient number of different recombinant cells are included to provide an ensemble of transcriptional regulatory elements of said organism sufficient to model the transcriptional responsiveness of said organism to a drug. In a preferred embodiment, the matrix is substantially comprehensive for the selected regulatory elements, e.g. essentially all of the gene promoters of the targeted organism are included." [cols. 6 – 7]

"In a preferred embodiment, the basal response profiles are determined. . . . The resultant electrical output signals are stored in a computer memory as genome reporter output signal matrix data structure associating each output signal with the coordinates of the corresponding microtiter plate well and the stimulus or drug. This information is indexed against the matrix to form reference response profiles that are used to determine the response of each reporter to any milieu in which a stimulus may be provided. After establishing a basal response profile for the matrix, each cell is contacted with a candidate drug. The term drug is used loosely to refer to agents which can provoke a specific cellular response. . . . The drug induces a complex response pattern of repression, silence and induction across the matrix . . . .The response profile reflects the cell's transcriptional adjustments to maintain homeostasis in the presence of the drug. . . . After contacting the cells with

the candidate drug, the reporter gene product signals from each of said cells is again measured to determine a stimulated response profile. The basal o[r] background response profile is then compared with . . . the stimulated response profile to identify the cellular response profile to the candidate drug." [cols. 7 – 8]

"In another embodiment of the invention, a matrix [i.e., array] of hybridization probes corresponding to a predetermined population of genes of the selected organism is used to specifically detect changes in gene transcription which result from exposing the selected organism or cells thereof to a candidate drug. In this embodiment, one or more cells derived from the organism is exposed to the candidate drug in vivo or ex vivo under conditions wherein the drug effects a change in gene transcription in the cell to maintain homeostasis. Thereafter, the gene transcripts, primarily mRNA, of the cell or cells is isolated . . . [and] then contacted with an ordered matrix [array] of hybridization probes, each probe being specific for a different one of the transcripts, under conditions where each of the transcripts hybridizes with a corresponding one of the probes to form hybridization pairs. The ordered matrix of probes provides, in aggregate, complements for an ensemble of genes of the organism sufficient to model the transcriptional responsiveness of the organism to a drug. . . . The matrix-wide signal profile of the drug-stimulated cells is then compared with a matrix-wide signal profile of negative control cells to obtain a specific drug response profile." [col. 8]

"The invention also provides means for computer-based qualitative analysis of candidate drugs and unknown compounds. A wide variety of reference response profiles may be generated and used in such analyses." [col. 8]

"Response profiles for an unknown stimulus (e.g. new chemicals, unknown compounds or unknown mixtures) may be analyzed by comparing the new stimulus response profiles with response profiles to known chemical stimuli." [col. 9]

"The response profile of a new chemical stimulus may also be compared to a known genetic response profile for target gene(s)." [col. 9]

The August 11, 1997 press release from the '588 patent's assignee, Acacia Biosciences (now part of Merck) (reference "h" attached hereto), and the September 15, 1997 news report by Glaser, "Strategies for Target Validation Streamline Evaluation of Leads," *Genetic Engineering News* (reference "i" attached hereto), attest the commercial value of the methods and technology described and claimed in the '588 patent.

WO 97/13877 ("Measurement of Gene Expression Profiles in Toxicity Determinations"), published April 17, 1997, describes an expression profiling technology differing somewhat from the use of cDNA microarrays and differing from the genome reporter

matrix of the '588 patent; but the use of the data is analogous. As per its title, the reference describes use of expression profiling in toxicity determinations. In particular, and with emphasis added:

> "[T]he invention relates to a method for detecting and monitoring changes in gene expression patterns in in vitro and in vivo systems for determining the toxicity of drug candidates." [Field of the invention]
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> "An object of the invention is to provide a new approach to toxicity assessment based on an examination of gene expression patterns, or profiles, in in vitro or in vivo test systems." [page 3]
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> "Another object of the invention is to provide a rapid and reliable method for correlating gene expression with short term and long term toxicity in test animals." [page 3]
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> "The invention achieves these and other objects by providing a method for massively parallel signature sequencing of genes expressed in one or more selected tissues of an organism exposed to a test compound. An important feature of the invention is the application of novel . . . methodologies that permit the formation of gene expression profiles for selected tissues . . . . Such profiles may be compared with those from tissues of control organisms at single or multiple time points to identify expression patterns predictive of toxicity." [page 3]
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> "As used herein, the terms 'gene expression profile,' and 'gene expression pattern' which is used equivalently, means a frequency distribution of sequences of portions of cDNA molecules sampled from a population of tag-cDNA conjugates. . .. Preferably, the total number of sequences determined is at least 1000; more preferably, the total number of sequences determined in a gene expression profile is at least ten thousand." [page 7]
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> "The invention provides a method for determining the toxicity of a compound by analyzing changes in the gene expression profiles in selected tissues of test organisms exposed to the compound. . . . . Gene expression profiles derived from test organisms are compared to gene expression profiles derived from control organisms. . . . " [page 7]

In light of this and other evidence of the state of the art, one of ordinary skill in the toxicology arts would conclude that "[i]t is my opinion,[3] therefore, based on the state of the art in toxicology at least since the mid-1990s -- and as regards protein profiling, even earlier -- that disclosure of the sequence of a new gene or protein, with or without knowledge of its biological function, would have been sufficient information for a toxicologist to use the gene and/or protein in expression profiling studies in toxicology."[4]

Appellants' Showing Of Facts Overcomes The Board's Concern That The Utility of Expression Analysis Is Limited Solely to Microarray-Based Expression Analysis

The Board states that "merely using the claimed polynucleotides as a component of a microarray would not satisfy § 101's utility requirement, as it has been interpreted by the courts," Decision at 17, and that "[w]e find that the asserted utility of the claimed polynucleotides -- as a component of a microarray for monitoring gene expression -- does not satisfy the utility requirement of § 101," Decision at 24.

In response to the Board's concerns, Appellants have submitted facts showing that the utility of the claimed polynucleotides is not limited to merely serving as a component of a microarray for monitoring gene expression. Appellants' facts show, in addition: (1) how persons of ordinary skill in the art would have known to use, and known how to use, data generated by expression analysis using the claimed polynucleotides for toxicology assessments, in drug development, for molecular phenotyping, and for other uses, regardless of the polynucleotide's biological function; and (2) that the uses for the claimed polynucleotides are not limited to microarrays. Applying the Board's legal analysis to this evidence, appellants' claimed polynucleotides are patentably useful.

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3 "Use of the words 'it is my opinion' to preface what someone of ordinary skill in the art would have known does not transform the factual statements contained in the declaration into opinion testimony." *In re Alton*, 37 USPQ2d 1578, 1583 (Fed. Cir. 1996).

4 Declaration of Dr. John C. Rockett, ¶ 18.

With respect to the latter of these two factual propositions -- that the uses for the claimed polynucleotides as an expression probe are not limited to microarrays, appellants' expert declarants have this to say: "microarrays are by no means the only, nor the first, expression profiling tool. As I describe in detail in my *Xenobiotica* review, there are a number of other differential expression analysis technologies that precede the development of microarrays, some by decades, and that have been applied to drug metabolism and toxicology research, including: (1) differential screening; (2) subtractive hybridization, . . . ; (3) differential display; (4) restriction endonuclease facilitated analyses, including serial analysis of gene expression (SAGE) and gene expression fingerprinting; and (5) EST analysis."[5]

And as noted above, each of WO 95/21944, WO 95/20681, U.S. Pat. No. 5,569,588 and WO 97/13877 describes a different platform for measuring gene-specific expression levels; all are useful in providing expression profiles for use in drug development, toxicology assessment, and molecular phenotyping.

Appellants' Showing of Facts Overcomes The Board's Concern That Appellants' Invention Lacks "Specific Utility"

The Board goes on to address the issue of "specific utility": "Appellants have been required to identify a utility that is specific to the invention claimed, as opposed to one that would apply regardless of the specific properties of the claimed invention." Decision at 26 (emphasis in the original). It concludes that Appellants have failed to identify such a utility based on the facts before it, coupled with its own understanding of molecular biological techniques.

Appellants' submission of additional facts overcomes this concern. Those facts demonstrate that, far from applying ***regardless*** of the specific properties of the claimed invention, the utility of Appellants' claimed polynucleotides as gene-specific probes ***depends upon*** specific properties of the polynucleotides, that is, their nucleic acid sequences.

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[5] Declaration of Dr. John C. Rockett, ¶ 7.

"[E]ach probe on . . . [a "high density spotted microarray[]"], with careful design and sufficient length, and with sufficiently stringent hybridization and wash conditions, ***binds specifically*** and with minimal cross-hybridization, to the probe's cognate transcript"[6]; "[e]ach gene included as a probe on a microarray provides ***a signal that is specific to the cognate transcript***, at least to a first approximation."[7] Accordingly, "each additional probe makes an additional transcript newly detectable by the microarray, increasing the detection range, and thus versatility, of this analytical device for gene expression profiling"[8]; equally, "[e]ach new gene-specific probe added to a microarray thus increases the number of genes detectable by the device, increasing the resolving power of the device."[9]

Although not required for present purposes, it would be appropriate to state on the record here that the specificity of nucleic acid hybridization was well-established far earlier than the development of high density spotted microarrays in 1995, and indeed is the well-established underpinning of many, perhaps most, molecular biological techniques developed over the past 30 - 40 years.

Appellants' Showing Of Facts, Coupled With A Change In Procedural Posture, Overcome The Board's Treatment of Appellants' Microarray Claim

It is beyond debate that microarrays are useful as research tools, form the basis of a vibrant and competitive commercial industry, and have been acknowledged as useful by the PTO's issuance of patents to microarrays, methods of making microarrays, and methods of using microarrays. Appellants' showing of facts provides ample evidence to support these well-established propositions.

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6 Declaration of Dr. John C. Rockett, ¶ 10(i), emphasis added.

7 Declaration of Dr. Vishwanath R. Iyer, ¶ 7 (emphasis added). See the footnote at ¶ 7 for a slighty more "nuanced" view.

8 Declaration of Dr. John C. Rockett, ¶ 10(ii).

9 Declaration of Dr. Vishwanath R. Iyer, ¶ 7.

But with all claims designated to rise or fall together on Appeal, the Board affirmed rejection of all rejected claims, drawing no distinction in its Decision between Appellants' claim 33, drawn to a microarray, and Appellants' claims to polynucleotides.

In light of the well-established utility of microarrays, as further evidenced by Appellants' showing of facts, the Board's affirmance of the rejection of claim 33, drawn to a microarray, would have to imply that the addition of Appellants' SIGP-25 polynucleotides to a microarray ***deprives*** the microarray of all its utility -- vitiating, eliminating, negating and nullifying the known and well-established usefulness of the microarray. Appellants' showing of facts demonstrates that the contrary is true: each gene-specific probe newly added to a microarray increases its usefulness to the research community,[10] and its commercial value.[11]

On remand, the Examiner is both free to and is obliged to examine each claim on its own merits. Appellants amend claim 33 herein to more particularly point out and distinctly claim appellants' microarray invention, and submit that the showing of facts fully supports the patentable utility of the microarray claimed in amended claim 33.

Evidence In The Record Overcomes The Board's Concern That Utilities Predicated on the Biological Function of the Encoded Protein Have Not Been Established

Although the statute and case law make clear that the natural function of a protein neither fully defines nor completely constrains the legally cognizable utilities of a protein, or of the nucleic acid that encodes it, the logical inverse is not invariably true: utility may indeed validly derive from the known biological functions of a natural protein.

The Board notes that Appellants' claimed SIGP-25 nucleic acid is 99.2% identical to the polynucleotides encoding the human chemokine β-2,[12] yet does "not agree with Appellants

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10 See, *e.g.*, Iyer declaration ¶¶ 7 and 8; Rockett Declaration ¶ 17.

11 *See*, [Second] Declaration of Tod Bedilion.

12 U.S. Patent No. 5,981,231 (of record).

that the claimed polynucleotides have utility because the encoded protein has been identified as a putative chemokine," Decision at 10, principally because "[t]he evidence of record shows that chemokines have widely varying activities in vivo," Decision at 11.

But the very evidence cited by the Board clearly shows that Appellants' claimed SIGP-25 polynucleotides are 99.2% identical to a human chemokine that is well-established to be useful,[13] and alleged by the Examiner to be prior to Appellants' invention.

The fact that Appellants' claimed polynucleotides belong to a class or family of compounds -- chemokines -- having widely varying activities *in vivo,* does not itself vitiate the usefulness of a new member of that family.

In fact, as the Board held in a case in which multiple utilities relating to multiple biological effects of prostacyclins were claimed in a single pharmaceutical claim, so long as what is known in the art, coupled with the teaching of the specification, provides "fully adequate guidelines as to intended utilities and how the uses can be effected," such uses can be effected. Even if some experimentation is required to determine optimum conditions for particular uses "in order to achieve a particular biological response, such experimentation is not considered to be undue." *Ex parte Skuballa,* 12 USPQ2d 1570 (Bd. Pat. App. & Int. 1989).

Precedent Not Addressed By The Board Is Controlling In This Case

The Board asserts that "[a]lthough each gene in the microarray contributes to the data generated by the microarray overall, the contribution of a single gene -- its data point-- is only a tiny contribution to the overall picture," and that "[a] patentable utility divided by a thousand does not necessarily equal a thousand patentable utilities." Decision at 28.

The Court of Appeals for the Federal Circuit has made clear that even were the Board's conclusion that measurement of the level of expression of the claimed polypeptide only a

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[13] The utility of human chemokine β-2 is evidenced by the issuance of U.S. Patent No. 5,981,231 (of record), which is statutorily presumed to meet all patentability requirements of Title 35, U.S. Code, including 35 U.S.C. § 101.

"tiny contribution" to such picture, even such a pixel would assuredly suffice under 35 U.S.C. § 101.

> An invention is "useful" under section 101 if it is capable of providing some identifiable benefit. See *Brenner v. Manson*, 383 U.S. 519, 534 [148 USPQ 689] (1966); *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 [24 USPQ2d 1401] (Fed. Cir. 1992) ("to violate Section 101 the claimed device must be totally incapable of achieving a useful result") [emphasis added]; *Fuller v. Berger*, 120 F. 274, 275 (7th Cir. 1903) (test for utility is whether invention "is incapable of serving any beneficial end").

Juicy Whip v. Orange Bang Inc., 51 USPQ2d 1700 (Fed. Cir. 1999). "[T]he fact that an invention has only limited utility and is only operable in certain applications is not grounds for finding lack of utility." *Envirotech Corp. v. Al George, Inc.*, 730 F.2d 753, 762, 221 USPQ 473, 480 (Fed. Cir. 1984), quoted in *Stifftung v. Renishaw PLC*, 945 F.2d 1173, 1180, 20 USPQ2d 1094 (Fed. Cir. 1991).

CONCLUSION

Appellants respectfully submit that the showing of facts and claim amendments made herein under 37 C.F.R. § 1.196(b)(1) are fully sufficient to overcome the Board's concerns: applying the Board's own legal analysis to the facts made newly of record, and further applying to these facts controlling precedent that was not addressed by the Board, Appellants' claimed polynucleotide and microarray inventions should be found to have well-established utilities, any one of which is sufficient to satisfy 35 U.S.C. §§ 101 and 112, first paragraph.

To the extent that Appellants have not explicitly traversed one or more of Board's concerns, Appellants respectfully traverse those concerns for the reasons already made of record during appeal.

In view of the above amendments and remarks, Appellants submit that this application is in condition for allowance, which action is earnestly solicited. In the event that a telephone conference or in person interview might help to expedite prosecution, the Examiner is invited to contact the undersigned at the number provided below.

Applicants believe that no fee is due with this communication. However, if the USPTO determines that a fee is due, the Commissioner is hereby authorized to charge Deposit Account No. **09-0108.**

Respectfully submitted,

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